nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-18620-4 OPEN

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Versatile live-cell activity analysis platform for characterization of neuronal dynamics at single-cell and network level

Xinyue Yuan[1✉], Manuel Schröter[1], Marie Engelene J. Obien[1,2], Michele Fiscella[1,2], Wei Gong[1,2], Tetsuhiro Kikuchi[3], Aoi Odawara[4], Shuhei Noji[4], Ikuro Suzuki[4], Jun Takahashi[3], Andreas Hierlemann[1,5] & Urs Frey[1,2,5]

Chronic imaging of neuronal networks in vitro has provided fundamental insights into mechanisms underlying neuronal function. Current labeling and optical imaging methods, however, cannot be used for continuous and long-term recordings of the dynamics and evolution of neuronal networks, as fluorescent indicators can cause phototoxicity. Here, we introduce a versatile platform for label-free, comprehensive and detailed electrophysiological live-cell imaging of various neurogenic cells and tissues over extended time scales. We report on a dual-mode high-density microelectrode array, which can simultaneously record in (i) full-frame mode with 19,584 recording sites and (ii) high-signal-to-noise mode with 246 channels. We set out to demonstrate the capabilities of this platform with recordings from primary and iPSC-derived neuronal cultures and tissue preparations over several weeks, providing detailed morpho-electrical phenotypic parameters at subcellular, cellular and network level. Moreover, we develop reliable analysis tools, which drastically increase the throughput to infer axonal morphology and conduction speed.

SCAD: A SCAD device (SCAD, Stem Cell & Device Laboratory, Inc., Kyoto, Japan) is a nanofiber scaffold that can be used to attach neuronal cells to build 3D cell cultures[39]. By placing iPSC-derived human dopaminergic-neurons (Elixirgen Scientific, Baltimore, USA) that have been cultured on an SCAD device on the electrode array, we recorded APs from 3D tissue-like neuron cultures (3–4 cell layers, 50 µm thickness), which showed features that were different from those observed in 2D neuronal cultures (Fig. 3f). Moreover, we observed signals propagating along the membrane structure (Supplementary Movie 4), likely indicating APs traveling along axonal arbors. These propagating signals featured higher amplitudes (>100 µV) as compared to axonal signals in 2D iPSC-derived neuron cultures shown in Fig. 2c (signals amplitudes <50 µV). This larger signal amplitude may be a consequence of the membrane-like structure of the neuronal layers on the SCAD, which may act as an insulating layer on top of the electrode array and, therefore, help to amplify the signals[40]. The detection of propagating axonal signals over extended areas in raw HD-MEA data, without any averaging, has, to the best of our knowledge, not been demonstrated previously.

Nature Communications 11, Article number: 4854 (2020), pp.6.